

Appl. No. 09/916,017

Amdt. dated Thursday, June 19, 2003

Reply to Office Action of January 22, 2003

REMARKS/ARGUMENTS

Claims 1-16, 18-27 remain in the present application. Claims 1-9 have been withdrawn from consideration based on a restriction requirement. Claims 10-16, 18-27 remain under consideration. The Office Action, dated January 22, 2003, has been carefully considered. In Response to the Office Action, please consider the following remarks.

The claims have been amended to more clearly set forth the Applicants' contribution to the art. These do not introduce new matter into the disclosure of the invention. The basis for the amendments to the claims can be found in paragraphs 21, 25 and 52, of the specification.

By way of review, the present invention relates to a targeted treatment for cancer with low systemic toxicity. The invention relies on the fact that tumor cells display elevated levels of the translation initiation factor, eIF4E. The eIF4E protein has been previously shown to be rate-limiting in cells for the initiation of protein synthesis. The eIF4E protein binds to the 5' m7pppG cap structure common to polyadenylated mRNAs and is part of a larger translation initiation complex (eIF4F), which is thought to bind to the 5' cap, unwind secondary structure in the 5' untranslated region (5' UTR) of mRNAs, and facilitate identification of the AUG initiation codon and 40S ribosomal recruitment and positioning. Messenger RNAs that contain sequences of long G/C rich 5' UTRs are poorly translated, including the vascular endothelial growth factor (VEGF) and fibroblast growth factor 2 (FGF2) mRNAs. In cells overexpressing eIF4E, VEGF and FGF2 mRNAs are efficiently translated.

The novel aspect of this technology is the ability to specifically effect tumor cells -- *without relying upon any targeting of the material itself* -- while leaving normal cells relatively unscathed. This represents a *significant advance* for therapy of solid tumors.

Appl. No. 09/916,017

Amdt. dated Thursday, June 19, 2003

Reply to Office Action of January 22, 2003

Rejections under 35 U.S.C. 112, Second Paragraph

Claims 23, 25, 26, and 27 were rejected, under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that the Applicants regard as the invention.

The Examiner has objected to claim 23 for reciting the phrase "the vector of claim 21" since there is insufficient antecedent basis for this limitation in the claim. The Examiner has also objected to claim 25 for depending on claim 23. Claim 23 has now been amended to recite "the vector of claim 22" for proper antecedent basis.

The Examiner has objected to claim 26 for reciting the phrase "the vector of claim 21" since there is insufficient antecedent basis for this limitation in the claim. Claim 26 has now been amended to recite "the vector of claim 22" for proper antecedent basis.

The Examiner has objected to claim 27 for reciting the phrase "the pharmaceutical composition of claim 25" since there is insufficient antecedent basis for this limitation in the claim. Claim 27 has now been amended to recite "the pharmaceutical composition of claim 26" for proper antecedent basis.

Claim Rejections under 35 U.S.C. 102

The Examiner has rejected claims 10, 11, 13, 14, 17, 18 and 22 under 35 U.S.C. §102(b) as being anticipated by Shimogori *et al.* (BBRC Vol. 223:544-548; 1996). The Shimogori *et al.* reference describes a specific sequence derived from the ornithine decarboxylase 5'UTR that specifically responds to the level of polyamines for translation, an example of auto-regulation of translation that does not pertain to the present invention's use of 5'UTR's that respond to levels of eIF4E.

Applicants submit that the 5'UTR described does not apply to the present invention as it does not contain each and every limitation required by the present claims. Specifically, the Shimogori *et al.* reference does not provide for a 5'UTR sequence that when placed in front of the open reading frame, forms a stable secondary structure that (i) substantially inhibits translation of the open reading frame (toxin) sequence under conditions that exist within normal mammalian cells that do not overexpress eukaryotic initiation factor eIF4E; (ii) substantially allows translation of

Appl. No. 09/916,017

Amdt. dated Thursday, June 19, 2003

Reply to Office Action of January 22, 2003

the open reading frame (toxin) sequence under conditions that exist within mammalian cells that overexpress eukaryotic initiation factor eIF4E relative to normal cells and (iii) has a secondary structure conformation having a stability of $\Delta G \geq$ about 50 Kcal/Mol.

While the Shimogori *et al.* reference describes a 188 bp sequence that does not encompass the full 5'UTR of ODC, which was found to respond to the eIF4E level (rev. in De Benedetti and Harris, 1999), such sequence does not provide the appropriate level of stability ($\Delta G \geq$ about 50 Kcal/Mol) and change in action in the presence of eIF4E to selectively regulate translation of the open reading frame.

In analyzing the sequence (see attached declaration by DeBenedetti), the only stem of possible stability is the 47 nucleotide marked as hatched boxes in the model on page 820 of the paper listed as "cgggguuuggcggggcgccuccaugggucaggccagccgggcccaccc." Some bulges and G-U base pairs destabilize that structure. Upon calculation of stability, the 5'UTR described by Shimogori would provide a secondary structure conformation having a stability of ΔG about -22 Kcal/Mol, less than that required by the current invention.

In addition, the 56% G/C-rich construct described is barely above the average distribution of G/C content. This is negligible in terms of increased stability. For comparison, the FGF 5'UTR used as an example in the present invention is 76% G/C-rich, offering a much higher level of stability.

The Shimogori *et al.* reference shows that low levels of polyamines stimulate translation of an mRNA open reading frame when preceded by a 188 nt G/C rich region of the 5'UTR of ODC. This system was tested only *in vitro* in rabbit reticulocyte lysates. It should be noted that rabbit reticulocyte lysates already contain elevated levels of eIF4E (Rau, M., Ohlmann, T., Morley, S. J., and Pain, V. M. (1996), J. Biol. Chem. 271(15), 8983-8990; reference attached). Despite that, the translation of the reporter construct with the ODC 5'UTR was still inhibited. Therefore, the Shimogori *et al.* reference contradicts, or teaches away from, the conception of the regulation of a suicide gene by art. Otherwise the pGC-TK construct would have been translated well in the absence of polyamines

Appl. No. 09/916,017
Amdt. dated Thursday, June 19, 2003
Reply to Office Action of January 22, 2003

The particular region of ODC described by the Shimogori *et al.* reference is insufficient to confer regulation by the level of eIF4E as shown by Shantz LM, Pegg AE. (Int J Biochem Cell Biol. 1999, 31(1):107-22. Review; see reference attached).

In summary, the Shimogori reference only presents a construction of a TK reporter that resembles some of the characteristic that are claimed in the present invention.

In the Examiner's Response to Arguments section, the Examiner also mentions that "[i]t is noted that the prior art indicates that the 5'UTR of Spi-1 comprises a 151 bp GC-rich region that inhibits translation in cells with low levels eIF4E and allows translation in cells that overexpress eIF4E (see van der Velden *et al.* 1999, cite in IDS, Table 1, p. 90)." As explained in the earlier telephonic conference, the 151 bp sequence described in the van der Velden *et al.* reference was never shown to be regulated by eIF4E. They only found that this mRNA is translationally repressed in reticulocyte lysates and does not indicate in any way that the 5'UTR could regulate translation in response to high and low concentrations of eIF4E within cells, as used in the present invention.

In light of this, it is submitted that the claims of the present application, as amended herein, are patentable over the references cited by the Examiner, and it is respectfully requested that the rejection under 35 U.S.C. 102(a) be withdrawn.

Claim Rejections Under 35 U.S.C. 103

The Examiner rejected claims 10, 11, 13, 14, 17, 18, 20, 21, 22, 24 and 26 under 35 U.S.C. §103(a) as being unpatentable over Koromilas *et al.* (EMBO 1992, cited in IDS) in view of Li B.D. *et al.* (Cancer 1997, cited in IDS) and further in view of Anderson L.M. *et al.* (Gene Therapy 1999, cited in IDS). Applicants respectfully traverse this rejection. The Koromilas *et al.* reference, in combination with the Li and Anderson references, do not in any way suggest the constructs of the present invention.

The Koromilas *et al.* reference describes the possible control by eIF4E but never shows if acted through translational or transcriptional control. The paper of Koromilas, 1992, is indicative that when a putative sequence with a ΔG of about -50 Kcal/mole was inserted at the 5'UTR of a PSV2CAT construct, expression of CAT

Appl. No. 09/916,017
Amdt. dated Thursday, June 19, 2003
Reply to Office Action of January 22, 2003

(only measured as activity) was reduced in control cells, but not in cells overexpressing eIF4E.

This reference only speculates that repression of eIF4E facilitates the translation of mRNAs containing excess secondary structure in their 5' non-coding region. However, Koromilas did not measure the levels of CAT mRNA expressed from the various vectors. It is possible that instead, they overexpress a transcription factor that overcomes an inhibition of transcription caused by the introduction of synthetic oligonucleotides upstream of the CAT ORF, thereby contradicting the idea of translational regulation. Koromilas showed that when put 4E into cells, they are transformed but this could be by a factor other than 4E. The bottom line is that he doesn't know the mechanism.

Even assuming, *inter alia*, that the assumptions of the Koromilas *et al.* reference were correct in their assumption, this reference only shows that this "may be one mechanism by which eIF4E regulates cell growth and transform cells in culture." The Koromilas *et al.* reference explicitly describes in column one, page 4157, that "[b]ased on our data, it is *possible* that eIF4E over expression facilitates the expression of genes regulating cell growth at the level of translation initiation." (emphasis added) It is a great leap from such postulations to the present invention as currently claimed.

The authors of that paper never measured the level of CAT mRNA expressed from their various vectors to ensure that it would be similar for each of the transfections they carried out. Therefore, it is entirely possible that the sequence they inserted downstream of the PSV2 promoter, but upstream of the Open Reading Frame (ORF) could interfere with transcription of the CAT mRNA, instead of its translation. No solid conclusions could be drawn from that paper, unlike the present application in which the applicants did measure the expression of the constructs at the mRNA level. In the case of the Koromilas' paper, the cells they used overexpressing eIF4E were also transformed.

Furthermore, at the time that paper was published, it was not known that most cancer cells overexpress the translation factor eIF4E, and as such, the utility of that paper in the design a suicide system that would preferentially attack cancer cells with no harm to normal tissues was nonexistent at that time. Even more importantly, it

Appl. No. 09/916,017
Amdt. dated Thursday, June 19, 2003
Reply to Office Action of January 22, 2003

could not be predicted that most "normal" cell lines and tissues in a body would have levels of eIF4E that are insufficient to allow translation of a mRNA preceded by a 5'UTR with a stability of 50 Kcal/mole.

The Li BD *et al.* reference describes only that eIF4E is elevated in breast carcinomas in comparison to normal breast. However, in order to produce the present invention, eIF4E would have to be low in all normal tissues and organs in the body, not only breast. Until the present applicants actually did the work in live mice, there was no way of telling that there would be sufficient discrimination at the level of translation to prevent translation of the toxin in various normal tissues.

As described by the Examiner, the Anderson L.M. *et al.* reference teaches only that a herpes thymidine kinase (TK) gene may be used as a "suicide gene" when expressed in certain tissues, e.g., breast tissue. This premise is well known in the art. The Anderson L.M. *et al.* reference does not deal with translational regulation at all.

In order to reject a patent application under section 103 using a combination of prior art, there must be some reason, suggestion, or motivation found in the prior art whereby a person of ordinary skill would make the combination. Applicants contend that there would have been no motivation to have combined the Koromilas *et al.*, Li B.D. *et al.* and Anderson L.M. *et al.* references as the Examiner suggests.

First, a motivation to further study the functions of a product is not the correct standard. There would have been no motivation to combine the references to create the present invention since it would not have been known that such a construct could be used specifically for regulatory control within a tumor cell. The Examiner cannot make a *prima facie* case of obviousness if it would not have been known at the time the invention was made that the presence or absence of eIF4E would selectively regulate such a control region.

It would have been totally speculative that the suicide gene expression system of the current invention would actually work *in vivo* in animals to turn on expression within tumor cells without turning on within normal cells.

In determining whether the prior art suggested the invention of the present application, it must be determined whether not the result achieved would have been sought. If there was no motivation to make the invention, there could be no suggestion

Appl. No. 09/916,017
Amdt. dated Thursday, June 19, 2003
Reply to Office Action of January 22, 2003

of a combination. In the present case, applicants show unexpected results in that the present compound acts only within cells having appropriate levels of eIF4E without harming the other, native cells in the subject.

The present invention is not obvious because it required more than ordinary skill to identify the source of a known problem in the art. While the known problem was that of treating tumor cells within a subject, it was not known that appropriately elevated levels of eIF4E could be found only within tumor cells and not within other cells throughout the subject.

Applicants have now found that appropriately elevated levels of eIF4E exist only within the tumor cells sought to be treated and did not exist in appropriate levels within other normal cells throughout the subject.

In addition, there must have been an obvious way of reaching the desired result. Thus, even where it might have been evident that one would want to specifically target tumor cells, considerable uncertainty as to whether the presence invention would work *in vivo* existed at the time the invention was made.

Classical gene therapies employ constitutive and/or tissue-specific promoters to direct the expression of the therapeutic gene within the tissue/cells of interest. Toxin based gene therapeutics depend upon the selective expression of a toxin within the target cells. Selective targeting of tumors for GEDPT/toxin methodologies is most often achieved by either direct injection of the gene therapeutic into the tumor mass or by systemic injection of a viral targeting vector. However, if one could develop a systemically introduced, pan-tumor-specific (versus tissue-specific) GEDPT approach (*i.e.* one with the potential to be applicable to the treatment of all tumors classes and sub-types) with high efficacy and reduced systemic toxicity, there are many technical hurdles to overcome.

Specifically, one skilled in the art would need to consider what consistent tumor cell trait might provide the specificity and selectivity to develop such an invention (*i.e.* what shared trait of tumor cells would provide selectivity and specificity of action)? From the numerous translational regulatory mechanisms including conventional scanning; upstream open-reading frame based inhibition; and internal ribosome entry), one skilled in the art would need to consider which might provide a

Appl. No. 09/916,017
Amdt. dated Thursday, June 19, 2003
Reply to Office Action of January 22, 2003

suitable *translationally-based* regulatory mechanism for the basis of this novel technology platform? Then, one would need to consider whether not this regulatory mechanism function within eukaryotic cells (*i.e.* how can one mediate the specific and selective translational expression of a gene product solely within tumor cells?)

While the 5'UTR's / eIF4E-dependent regulation of a therapeutic gene provides one mechanism of providing the specificity and selectivity of protein product expression desired, one would need to consider what other translational-regulatory mechanisms are known that might modulate/alter any anticipated/desired outcome. (*E.g.*, differential eIF4E phosphorylation and/or differential expression of additional regulatory factors, *etc.*, between normal tissues and cancerous tissues) In addition, one would need to consider that as high levels of eIF4E enhance the expression of alternative translational start sites, *e.g.*, how does the phosphorylation status of eIF4E and associated regulatory factors impact these events?

While the prior art shows *in vitro* analyses employing an optimized translation system (rabbit reticulocyte lysates), which have been determined to contain super-optimal amounts of eIF4E, it would not have been known if similar non-cancer specific (and yet unidentified) expression of eIF4E in selected tissues (or during tissue development) would impair the ability of this system to work *in vivo*.

The present invention provides a post-transcriptional, translationally based selective and specific (and multi-functional) gene expression vector. This represents an inventive identification and deployment of several sets of highly complex technology bases including post-transcriptional, translational regulatory mechanisms; cancerous cell phenotype technologies and gene therapy technologies, none which in and of itself provides sufficient direction for the successful development, reduction to practice *in vitro* and subsequent *in vivo* demonstration of proof-of-concept/efficacy as achieved by the presence inventors.

The Examiner has rejected claims 10, 13, 14, 17, and 18, under 35 U.S.C. §103(a) as being unpatentable over Koromilas *et al.* (EMBO 1992, cited in IDS) in view of Li B.D. *et al.* (Cancer 1997, cited in IDS) and of Anderson L.M. *et al.* (Gene Therapy 1999, cited in IDS), and further in view of Willis (Int. Journ. Biochem. Cell. Biol., 1999, cited in IDS). Applicants respectfully traverse this rejection. The

Appl. No. 09/916,017
Amtd. dated Thursday, June 19, 2003
Reply to Office Action of January 22, 2003

Koromilas *et al.* reference, in combination with the Li and Anderson references, do not in any way suggest the constructs of the present invention, as described above. The further addition of the Willis reference does not in anyway suggest the current invention. In fact, the Willis reference teaches away from the present invention.

Regarding the Willis reference, the Examiner has misinterpreted what Willis has stated. Starting with page 79 of the review, it is Willis' contention that mRNA of c-myc, FGF-2 and PDGF contain internal ribosome entry segments in addition to be occasionally translated by a cap-dependent mechanism. In particular, translation FGF-2 (our choice of UTR) was described on page 82 to be driven by an IRES and thus be cap-independent for translation. The Examiner has misquoted the Willis reference in stating that one of the four features that the group of mRNAs share is that they are translated in a cap-dependent manner. However, as described above, Willis states that the translation was cap-independent and that was IRES dependent. Therefore, there were discrepancies in the published literature, and this made the choice of the FGF-2 5'UTR unpredictable in our suicide system approach.

Willis also never said that FGF2 translation occurs "in pancreatic tumor cells because translational repression of the 5UTR is relieved in cells which overexpress cIF4E". She actually states that FGF2 is translated via an IRES, which is contrary to what the current applicants have demonstrated, and contradict the discovery of the current patent invention. Therefore, the addition of the Willis reference actual acts to teach away from the current invention.

The Examiner has rejected claims 10, 22, 23 and 25 under 35 U.S.C. §103(a) as being unpatentable over Shimogori *et al.* (BBRC Vol. 223:544-548; 1996) in view of DeBenedetti *et al.* (Nucleic Acids Research, 1991; 8:1924-1931, cited in IDS). Applicants respectfully traverse this rejection. The Shimogori *et al.* reference, in combination with the DeBenedetti *et al.* reference, does not in any way suggest the present invention as described in the currently amended claims.

Adding the DeBenedetti *et al.* reference in combination of the Shimogori *et al.* reference would not have made the present invention obvious. As described above, the sequence described by the Shimogori *et al.* reference does not provide the appropriate

Appl. No. 09/916,017
Amdt. dated Thursday, June 19, 2003
Reply to Office Action of January 22, 2003

level of stability ($\Delta G \geq$ about 50 Kcal/Mol) and change in action in the presence of eIF4E to selectively regulate translation of the open reading frame.

The DeBenedetti *et al.* reference merely describes a BK virus-based episomal vector for expression of foreign genes within mammalian cells. This vector and others have been well known in the art for more than a decade. As with the other references, such combination of references does not provide all the elements of the present invention and as such, lack critical elements. The particular region of ODC described by the Shimogori *et al.* reference is insufficient to confer regulation by the level of eIF4E and its combination with the DeBenedetti *et al.* reference does not overcome this deficiency.

Even if such references included all the necessary elements of the present invention (which it does not), the present invention represents an inventive identification and deployment of several sets of highly complex technological advances that one skilled in the art would not have had a motivation to combine, as described above in regards to the Koromilas *et al.* reference.

In summary, combining the Shimogori reference with the DeBenedetti *et al.* reference only presents a construction of a TK reporter that resembles some of the characteristic that are claimed in the present invention.

The Examiner rejected claims 10, 22, 26 and 27 under 35 U.S.C. §103(a) as being unpatentable over Shimogori *et al.* (BBRC Vol. 223:544-548; 1996) in view of GIBCO/BRL (1993-1994 catalog, p. 9-19 only). Applicants respectfully traverse this rejection. The Shimogori *et al.* reference, in combination with the GIBCO/BRL reference, does not in any way suggest the present invention as described in the currently amended claims.

Adding the GIBCO/BRL reference in combination of the Shimogori *et al.* reference would not have made the present invention obvious. The GIBCO/BRL reference merely presents information about transfection reagents.

The present invention is not obvious in light of these references because it was not known that such a construct could be formed that would work *in vivo*. It was not known that appropriately elevated levels of eIF4E could be found only within tumor cells and not within other cells throughout the subject.

Appl. No. 09/916,017
Amdt. dated Thursday, June 19, 2003
Reply to Office Action of January 22, 2003

In addition, there must have been an obvious way of reaching the desired result. Thus, even where it might have been evident that one would want to specifically target tumor cells, considerable uncertainty as to whether the presence invention would work *in vivo* existed at the time the invention was made.

The Examiner has rejected claims 10, 22, 23 and 25, under 35 U.S.C. §103(a) as being unpatentable over Koromilas *et al.* (EMBO 1992, cited in IDS) in view of Li B.D. *et al.* (Cancer 1997, cited in IDS) and of Anderson L.M. *et al.* (Gene Therapy 1999, cited in IDS), and further in view of DeBenedetti *et al.* (Nucleic Acids Research, 1991; 8:1924-1931, cited in IDS). Applicants respectfully traverse this rejection. The Koromilas *et al.* reference, in combination with the Li and Anderson references, do not in any way suggest the constructs of the present invention, as described above. The further addition of the DeBenedetti *et al.* reference does not in anyway suggest the current invention. Furthermore, the Examiner has rejected claims 10, 13, 14, 17, and 18, under 35 U.S.C. §103(a) as being unpatentable over Koromilas *et al.* (EMBO 1992, cited in IDS) in view of Li B.D. *et al.* (Cancer 1997, cited in IDS), and of Anderson L.M. *et al.* (Gene Therapy 1999, cited in IDS), and further in view of GIBCO/BRL (1993-1994 catalog, p. 9-19 only). Applicants respectfully traverse this rejection. The Koromilas *et al.* reference, in combination with the Li and Anderson references, do not in any way suggest the constructs of the present invention, as described above. The further addition of the GIBCO/BRL reference does not in anyway suggest the current invention.

As already described above, the Koromilas *et al.* reference merely speculates that over-expression of eIF4E facilitates the translation of mRNAs containing excess secondary structure in their 5' non-coding region. However, Koromilas did not determine whether or not they overexpress a transcription factor that overcomes an inhibition of transcription caused by the introduction of synthetic oligonucleotides upstream of the CAT ORF, thereby contradicting the idea of translational regulation. Koromilas showed that when put eIF4E into cells, they are transformed but this could be by a factor other than eIF4E.

The Koromilas *et al.* reference explicitly describes in column one, page 4157, that "[b]ased on our data, it is possible that eIF4E over expression facilitates the

Appl. No. 09/916,017
Amdt. dated Thursday, June 19, 2003
Reply to Office Action of January 22, 2003

expression of genes regulating cell growth at the level of translation initiation.”
(emphasis added) No solid conclusions could be drawn from that paper, unlike the present application in which the applicants did measure the expression of the constructs at the mRNA level. In the case of the Koromilas’ paper, the cells they used overexpressing eIF4E were also transformed.

There would have been no motivation to combine the references cited by the Examiner to create the present invention since it would not have been known that such a construct could be used specifically for regulatory control within a tumor cell.

At the time of the present invention, it was not known that most cancer cells overexpress the translation factor eIF4E, and as such, the utility of a suicide system that would preferentially attack cancer cells based on eIF4E regulation with no concomitant harm to normal tissues was nonexistent at that time. Even more importantly, it could not be predicted that most “normal” cell lines and tissues in a body would have levels of eIF4E that are insufficient to allow translation of a mRNA preceded by a 5’UTR with a stability of 50 Kcal/mole. Applicants have now found that appropriately elevated levels of eIF4E exist only within the tumor cells sought to be treated and do not exist in appropriate levels within other normal cells throughout the subject.

There would have been no motivation to combine the references cited to create the present invention since it would not have been known that such a construct could be used specifically for regulatory control within a tumor cell using the presence or absence of eIF4E to selectively regulate such a control region. It would have been totally speculative that the suicide gene expression system of the current invention would actually work *in vivo* in animals to turn on expression within tumor cells without turning on within normal cells. In the present case, applicants show unexpected results in that the present compound acts only within cells having appropriate levels of eIF4E without harming the other, normal cells in the subject.

Finally, considerable uncertainty as to whether the present invention would work *in vivo* existed at the time the invention was made due to the many technical hurdles to overcome.

Appl. No. 09/916,017
Amdt. dated Thursday, June 19, 2003
Reply to Office Action of January 22, 2003

Accordingly, it is submitted that the rejection under 35 U.S.C. 103 is not applicable to the claims of the present invention, as amended herein, and it is respectfully requested that it be withdrawn.

Response to Previous Amendments/Arguments

Applicants appreciate Examiner's consideration of the previous rejections under 35 USC 112(1) and (2), as well as 35 USC 102(a) and 35 USC 103, which have now been withdrawn in view of the previous amendments and persuasive arguments.

Based on the foregoing amendments and remarks, as well as the attached Declaration under 37 CFR 1.132, it is submitted that the present application is now in form for allowance. Therefore, early reconsideration and allowance of the claims, as currently pending, are solicited.

The Assistant Commissioner for Patents is authorized to charge any deficiency or credit any overpayment to Frost Brown Todd LLC Deposit Account No. 06-2226.

Respectfully submitted,

DEBENEDETTI, Arrigo, *et al.*



By

Stephen R. Albainy-Jenei
Registration No. 41,487
Telephone (513) 651-6839
Facsimile (513) 651-6981
FROST BROWN TODD LLC
2200 PNC Center
201 East Fifth Street
Cincinnati, Ohio 45202-4182
salbainyjenei@fbtlaw.com

Appl. No. 09/916,017
Amdt. dated Thursday, June 19, 2003
Reply to Office Action of January 22, 2003

CERTIFICATION OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office on the date shown below:

Joyce O. Fields

(Type or print name of person signing certification)

Joyce O. Fields

Signature

6/19/03

Date

FAX Telephone No.:

703-308-4242

Attn:

J. Eric Angell

Art Unit No.:

1635

Serial No.

09/916,017

CinLibrary/1265911.3